



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 18-603/S-019

Food and Drug Administration
Rockville MD 20857

Glaxo Wellcome Inc.
Attention: Robert S. Watson
5 Moore Drive
Research Triangle Park, NC 27709

JUN 2 1998

Dear Mr. Watson:

Please refer to your May 30, 1997, supplemental New Drug Application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zovirax (acyclovir sodium) for Injection 500 mg and 1000 mg vials.

We acknowledge receipt of your submissions dated May 15, and May 29, 1998.

The User Fee goal date for this application is June 2, 1998.

This supplemental drug application provides for the treatment of herpes simplex virus infections in neonatal patients.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the June 2, 1998, draft labeling. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on June 2, 1998. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL and one copy on diskette as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 18-603/S-019. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Under section 736(a)(1)(B)(ii) of the Prescription Drug User Fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for this application. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the date of the invoice.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Should you have any questions, please contact Melissa M. Truffa, R.Ph., Regulatory Health Manager at (301) 827-2335.

Sincerely yours,

Heidi M. Jolson, M.D., M.P.H.
Director
Division of Anti-Viral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

JUN 2 1998

PRODUCT INFORMATION

ZOVIRAX^R
(acyclovir sodium)
for Injection

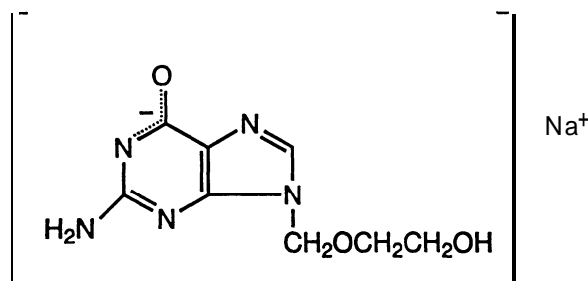
APPROVED

FOR INTRAVENOUS INFUSION ONLY

DESCRIPTION: ZOVIRAX is the brand name for acyclovir, a synthetic nucleoside analog active against herpesviruses. Acyclovir sodium for injection is a sterile lyophilized powder for intravenous administration only. Each 500-mg vial contains 500 mg of acyclovir and 49 mg of sodium, and each 1000-mg vial contains 1000 mg acyclovir and 98 mg of sodium. Reconstitution of the 500-mg or 1000-mg vials with 10 mL or 20 mL, respectively, of Sterile Water for Injection, USP results in a solution containing 50 mg/mL of acyclovir. The pH of the reconstituted solution is approximately 11. Further dilution in any appropriate intravenous solution must be performed before infusion (see DOSAGE AND ADMINISTRATION: Method of Preparation and Administration).

Acyclovir sodium is a white, crystalline powder with the molecular formula $C_8H_{10}N_5NaO_3$ and a molecular weight of 247.19. The maximum solubility in water at 25°C exceeds 100 mg/mL. At physiologic pH, acyclovir sodium exists as the un-ionized form with a molecular weight of 225 and a maximum solubility in water at 37°C of 2.5 mg/mL. The pKa's of acyclovir are 2.27 and 9.25.

The chemical name of acyclovir sodium is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6H-purin-6-one monosodium salt; it has the following structural formula:



VIROLOGY: Mechanism of Antiviral Action: Acyclovir is a synthetic purine nucleoside analogue with in vitro and in vivo inhibitory activity against herpes simplex virus types 1 (HSV-1), 2 (HSV-2), and varicella-zoster virus (VZV). In cell culture, acyclovir's highest antiviral activity is against HSV-1, followed in decreasing order of potency against HSV-2 and VZV.

The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV. This viral enzyme converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. In vitro, acyclovir triphosphate stops replication of herpes viral DNA. This is accomplished in three ways: 1) competitive inhibition of viral DNA polymerase, 2) incorporation into and termination of the growing viral DNA chain, and 3) inactivation of the viral DNA polymerase. The greater antiviral activity of acyclovir against HSV compared to VZV is due to its more efficient phosphorylation by the viral TK.

Antiviral Activities: The quantitative relationship between the in vitro susceptibility of herpes viruses to antivirals and the clinical response to therapy has not been established in humans, and virus -sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (IC₅₀) vary greatly depending upon a number of factors.

ZOVIRAX (acyclovir sodium) for Injection

Using plaque-reduction assays, the IC_{50} against herpes simplex virus isolates ranges from 0.02 to 13.5 mcg/mL for HSV-1 and from 0.01 to 9.9 mcg/mL for HSV-2. The IC_{50} for acyclovir against most laboratory strains and clinical isolates of VZV ranges from 0.12 to 10.8 mcg/mL. Acyclovir also demonstrates activity against the Oka vaccine strain of VZV with a mean IC_{50} of 1.35 mcg/mL.

Drug Resistance: Resistance of HSV and VZV to antiviral nucleoside analogues can result from qualitative or quantitative changes in the viral TK or DNA polymerase. Clinical isolates of HSV and VZV with reduced susceptibility to acyclovir have been recovered from immunocompromised patients, especially with advanced HIV infection. While most of the acyclovir-resistant mutants isolated thus far from such patients have been found to be TK-deficient mutants, other mutants involving the viral TK gene (TK partial and TK altered) and DNA polymerase have been isolated. TK-negative mutants may cause severe disease in infants and immunocompromised adults. The possibility of viral resistance to acyclovir should be considered in patients who show poor clinical response during therapy.

CLINICAL PHARMACOLOGY: Pharmacokinetics: The pharmacokinetics of acyclovir after intravenous administration have been evaluated in adult patients with normal renal function during Phase 1/2 studies after single doses ranging from 0.5 to 15 mg/kg and after multiple doses ranging from 2.5 to 15 mg/kg every 8 hours. Proportionality between dose and plasma levels is seen after single doses or at steady state after multiple dosing. Average steady-state peak and trough concentrations from 1-hour infusions administered every 8 hours are given in Table 1.

Table 1: Acyclovir Peak and Trough Concentrations at Steady State

Dosage Regimen	C_{max}^{SS}	C_{trough}^{SS}
5 mg/kg q 8 hr (n = 8)	9.8 mcg/mL range: 5.5 to 13.8	0.7 mcg/mL range: 0.2 to 1.0
10 mg/kg q 8 hr (n = 7)	22.9 mcg/mL range: 14.1 to 44.1	1.9 mcg/mL range: 0.5 to 2.9

Concentrations achieved in the cerebrospinal fluid are approximately 50% of plasma values. Plasma protein binding is relatively low (9% to 33%) and drug interactions involving binding site displacement are not anticipated.

Renal excretion of unchanged drug is the major route of acyclovir elimination accounting for 62% to 91% of the dose. The only major urinary metabolite detected is 9-carboxymethoxymethylguanine accounting for up to 14.1% of the dose in patients with normal renal function.

The half-life and total body clearance of acyclovir are dependent on renal function as shown in Table 2.

Table 2: Acyclovir Half-life and Total Body Clearance

Creatinine Clearance (mL/min per 1.73 m ²)	Half-Life (hr)	Total Body Clearance	
		(mL/min per 1.73 m ²)	(mL/min per kg)
>80	2.5	327	5.1
50 - 80	3.0	248	3.9
15 - 50	3.5	190	3.4
0 (Anuric)	19.5	29	0.5

ZOVIRAX (acyclovir sodium) for Injection

Special Populations: Adults With Impaired Renal Function: ZOVIRAX was administered at a dose of 2.5 mg/kg to six adult patients with severe renal failure. The peak and trough plasma levels during the 47 hours preceding hemodialysis were 8.5 mcg/mL and 0.7 mcg/mL, respectively.

Consult DOSAGE AND ADMINISTRATION section for recommended adjustments in dosing based upon creatinine clearance.

Pediatrics: Acyclovir pharmacokinetics were determined in 16 pediatric patients with normal renal function ranging in age from 3 months to 16 years at doses of approximately 10 mg/kg and 20 mg/kg every 8 hours (Table 3). Concentrations achieved at these regimens are similar to those in adults receiving 5 mg/kg and 10 mg/kg every 8 hours, respectively (Table 1). Acyclovir pharmacokinetics were determined in 12 patients ranging in age from birth to 3 months at doses of 5 mg/kg, 10 mg/kg, and 15 mg/kg every 8 hours (Table 3)

Table 3: Acyclovir Pharmacokinetics in Pediatric Patients (Mean \pm SD)

Parameter	Birth to 3 Months of Age (n = 12)	3 Months to 12 Years of Age (n = 16)
CL (mL/min per kg)	4.46 \pm 1.61	8.44 \pm 2.92
VDSS (L/kg)	1.08 \pm 0.35	1.01 \pm 0.28
Elimination Half-life (hours)	3.80 \pm 1.19	2.36 \pm 0.97

Drug Interactions: Coadministration of probenecid with acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.

Clinical Trials: Herpes Simplex Infections in Immunocompromised Patients: A multicenter trial of ZOVIRAX for Injection at a dose of 250 mg/m² every 8 hours (750 mg/m² per day) for 7 days was conducted in 98 immunocompromised patients (73 adults and 25 children) with orofacial, esophageal, genital, and other localized infections (52 treated with ZOVIRAX and 46 with placebo). ZOVIRAX decreased virus excretion, reduced pain, and promoted healing of lesions.

Initial Episodes of Herpes Genitalis: In placebo-controlled trials, 58 patients with initial genital herpes were treated with intravenous ZOVIRAX 5 mg/kg or placebo (27 patients treated with ZOVIRAX and 31 treated with placebo) every 8 hours for 5 days. ZOVIRAX decreased the duration of viral excretion, new lesion formation, and duration of vesicles, and promoted healing of lesions.

Herpes Simplex Encephalitis: Sixty-two patients ages 6 months to 79 years with brain biopsy-proven herpes simplex encephalitis were randomized to receive either ZOVIRAX (10 mg/kg every 8 hours) or vidarabine (15 mg/kg per day) for 10 days (28 were treated with ZOVIRAX and 34 with vidarabine). Overall mortality at 12 months for patients treated with ZOVIRAX was 25% compared to 59% for patients treated with vidarabine. The proportion of patients treated with ZOVIRAX functioning normally or with only mild sequelae (e.g., decreased attention span) was 32% compared to 12% of patients treated with vidarabine.

Patients less than 30 years of age and those who had the least severe neurologic involvement at time of entry into study had the best outcome with treatment with ZOVIRAX. An additional controlled study performed in Europe demonstrated similar findings.

Neonatal Herpes Simplex Virus Infection: Two hundred and two infants with neonatal herpes simplex infections were randomized to receive either ZOVIRAX 10 mg/kg every 8 hours (n = 107) or vidarabine 30 mg/kg per day (n = 95) for 10 days. Outcomes are presented in Table 4.

ZOVIRAX (acyclovir sodium) for Injection

Table 4: Mortality at 1 Year

HSV Disease Classification	Treatment Group	
	Acyclovir (n = 107)	Vidarabine (n = 95)
SEM* (n = 85)	0/54	0/31
CNS+ (n = 71)	5/35	5/36
DISS++ (n = 46)	11/18	14/28

* **SEM** refers to localized infection with disease limited to skin, eye, and/or mouth.

+CNS refers to infection of the central nervous system with compatible neurologic and CSF findings.

‡DISS refers to visceral organ involvement such as hepatitis or pneumonitis with or without CNS involvement.

Rates of neurologic sequelae at 1 year were comparable between the treatment groups.

Varicella-Zoster Infections in Immunocompromised Patients: A multicenter trial of ZOVIRAX for Injection at a dose of 500 mg/m² every 8 hours for 7 days was conducted in immunocompromised patients with zoster infections (shingles). Ninety-four (94) patients were evaluated (52 patients were treated with ZOVIRAX and 42 with placebo). ZOVIRAX was superior to placebo as measured by reductions in cutaneous dissemination and visceral dissemination.

INDICATIONS AND USAGE:

Herpes Simplex Infections in Immunocompromised Patients: ZOVIRAX for Injection is indicated for the treatment of initial and recurrent mucosal and cutaneous herpes simplex (HSV-1 and HSV-2) in immunocompromised patients.

Initial Episodes of Herpes Genitalis: ZOVIRAX for Injection is indicated for the treatment of severe initial clinical episodes of herpes genitalis in immunocompetent patients.

Herpes Simplex Encephalitis: ZOVIRAX for Injection is indicated for the treatment of herpes simplex encephalitis.

Neonatal Herpes Simplex Virus Infection: ZOVIRAX for Injection is indicated for the treatment of neonatal herpes infections.

Varicella-Zoster Infections in Immunocompromised Patients: ZOVIRAX for Injection is indicated for the treatment of varicella-zoster (shingles) infections in immunocompromised patients.

CONTRAINDICATIONS: ZOVIRAX for Injection is contraindicated for patients who develop hypersensitivity to acyclovir or valacyclovir.

WARNINGS: ZOVIRAX for Injection is intended for intravenous infusion only, and should not be administered topically, intramuscularly, orally, subcutaneously, or in the eye. Intravenous infusions must be given over a period of at least 1 hour to reduce the risk of renal tubular damage (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal failure, in some cases resulting in death, has been observed with acyclovir therapy (see ADVERSE REACTIONS: Observed During Clinical Practice and OVERDOSAGE).

Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), which has resulted in death, has occurred in immunocompromised patients with high exposures to acyclovir.

PRECAUTIONS:

ZOVIRAX (acyclovir sodium) for Injection

General: Precipitation of acyclovir crystals in renal tubules can occur if the maximum solubility of free acyclovir (2.5 mg/mL at 37°C in water) is exceeded or if the drug is administered by bolus injection. Ensuing renal tubular damage can produce acute renal failure.

Abnormal renal function (decreased creatinine clearance) can occur as a result of acyclovir administration and depends on the state of the patient's hydration, other treatments, and the rate of drug administration. Concomitant use of other nephrotoxic drugs, pre-existing renal disease, and dehydration make further renal impairment with acyclovir more likely.

Administration of ZOVIRAX by intravenous infusion must be accompanied by adequate hydration.

When dosage adjustments are required, they should be based on estimated creatinine clearance (see DOSAGE AND ADMINISTRATION).

Approximately 1% of patients receiving intravenous acyclovir have manifested encephalopathic changes characterized by either lethargy, obtundation, tremors, confusion, hallucinations, agitation, seizures, or coma. ZOVIRAX should be used with caution in those patients who have underlying neurologic abnormalities and those with serious renal, hepatic, or electrolyte abnormalities, or significant hypoxia.

Drug Interactions: See CLINICAL PHARMACOLOGY: Pharmacokinetics.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The data presented below include references to peak steady-state plasma acyclovir concentrations observed in humans treated with 30 mg/kg per day (10 mg/kg every 8 hours, dosing appropriate for treatment of herpes zoster or herpes encephalitis), or 15 mg/kg per day (5 mg/kg every 8 hours, dosing appropriate for treatment of primary genital herpes or herpes simplex infections in immunocompromised patients). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. At 450 mg/kg per day, plasma concentrations in both the mouse and rat bioassay were lower than concentrations in humans.

Acyclovir was tested in 16 genetic toxicity assays. No evidence of mutagenicity was observed in four microbial assays. Acyclovir demonstrated mutagenic activity in two in vitro cytogenetic assays (one mouse lymphoma cell line and human lymphocytes). NO mutagenic activity was observed in five in vitro cytogenetic assays (three Chinese hamster ovary cell lines and two mouse lymphoma cell lines).

A positive result was demonstrated in one of two in vitro cell transformation assays, and morphologically transformed cells obtained in this assay formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. No activity was demonstrated in another, possibly less sensitive, in vitro cell transformation assay.

Acyclovir caused chromosomal damage in Chinese hamsters at 31 to 61 times human dose levels. In rats, acyclovir produced a nonsignificant increase in chromosomal damage at five to 10 times human levels. No activity was observed in a dominant lethal study in mice at three to six times human levels.

Acyclovir did not impair fertility or reproduction in mice (450 mg/kg per day, PO) or in rats (25 mg/kg per day, SC). In the mouse study, plasma levels were the same as human levels, while in the rat study, they were

one to three times human levels, respectively) implantation efficacy, but not litter size, was decreased. In a rat peri- and post-natal study at 50 mg/kg per day, SC, there was a statistically significant decrease in group mean numbers of corpora lutea, total implantation sites, and live fetuses.

No testicular abnormalities were seen in dogs given 50 mg/kg per day, IV for 1 month (one to three times human levels) or in dogs given 60 mg/kg per day orally for 1 year (the same as human levels). Testicular atrophy and aspermatogenesis were observed in rats and dogs at higher dose levels.

ZOVIRA® (acyclovir) sodium) for injection

Pregnancy: Teratogenic Effects: Pregnancy Category B. Acyclovir was not teratogenic in the mouse (450 mg/kg per day, PO), rabbit (50 mg/kg per day, SC and IV), or rat (50 mg/kg per day, SC). These exposures resulted in plasma levels the same as, four and nine, and one and two times, respectively, human levels.

There are no adequate and well-controlled studies in pregnant women. A prospective epidemiologic registry of acyclovir use during pregnancy has collected data since June 1984. As of December 1997, outcomes of live births have been documented in 552 women exposed to systemic acyclovir during the first trimester of pregnancy. The occurrence rate of birth defects approximates that found in the general population. However, the small size of the registry is insufficient to evaluate the risk for specific defects or to permit definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses. Acyclovir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Acyclovir concentrations have been documented in breast milk in two women following oral administration of ZOVIRAX and ranged from 0.6 to 4.1 times corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg per day. ZOVIRAX should be administered to a nursing mother with caution and only when indicated.

Geriatric Use: Clinical studies of ZOVIRAX did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased renal function, and of concomitant disease or other drug therapy.

Pediatric Use: See DOSAGE AND ADMINISTRATION.

ADVERSE REACTIONS: The adverse reactions listed below have been observed in controlled and uncontrolled clinical trials in approximately 700 patients who received ZOVIRAX at -5 mg/kg (250 mg/m²) three times daily, and approximately 300 patients who received -10 mg/kg (500 mg/m²) three times daily.

The most frequent adverse reactions reported during administration of ZOVIRAX were inflammation or phlebitis at the injection site in approximately 9% of the patients, and transient elevations of serum creatinine or BUN in 5% to 10% (the higher incidence occurred usually following rapid [less than 10 minutes] intravenous infusion). Nausea and/or vomiting occurred in approximately 7% of the patients (the majority occurring in nonhospitalized patients who received 10 mg/kg). Itching, rash, or hives occurred in approximately 2% of patients. Elevation of transaminases occurred in 1% to 2% of patients.

The following hematologic abnormalities occurred at a frequency of less than 1%: anemia, neutropenia, thrombocytopenia, thrombocytosis, leukocytosis, and neutrophilia. In addition, anorexia and hematuria were observed.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of ZOVIRAX for Injection in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, potential causal connection to ZOVIRAX or a combination of these factors.

General: Anaphylaxis, fever, headache, pain, peripheral edema.

Digestive: Diarrhea, elevated liver function tests, gastrointestinal distress, nausea.

Cardiovascular: Hypotension.

Hemic and Lymphatic: Disseminated intravascular coagulation, hemolysis, leukopenia, lymphadenopathy.

Musculoskeletal: Myalgia.

ZOVIRAX (acyclovir sodium) for Injection

Nervous: Agitation, coma, confusion, dizziness, delirium, hallucinations, obtundation, psychosis, seizure, somnolence. (These symptoms may be marked, particularly in older adults.) (See PRECAUTIONS.)

Skin: Alopecia, erythema multiforme, pruritus, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria.

Special Senses: Visual abnormalities.

Urogenital: Renal failure, elevated blood urea nitrogen, elevated creatinine (see WARNINGS).

OVERDOSAGE: Overdosage has been reported following administration of bolus injections, or inappropriately high doses, and in patients whose fluid and electrolyte balance was not properly monitored. This has resulted in elevations in BUN, serum creatinine, and subsequent renal failure. Lethargy, convulsions, and coma have been reported. Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) is exceeded in the intratubular fluid. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION: CAUTION-RAPID OR BOLUS INTRAVENOUS INJECTION MUST BE AVOIDED (see WARNINGS and PRECAUTIONS).

INTRAMUSCULAR OR SUBCUTANEOUS INJECTION MUST BE AVOIDED (see WARNINGS).

Therapy should be initiated as early as possible following onset of signs and symptoms of herpes infections.

A maximum dose equivalent to 20 mg/kg every 8 hours should not be exceeded for any patient.

Dosage: Herpes Simplex Infections: Mucosal and Cutaneous Herpes Simplex (HSV-1 and HSV-2) Infections in Immunocompromised Patients:

Adults and Adolescents (72 years of age and older): 5 mg/kg infused at a constant rate over 1 hour, every 8 hours for 7 days.

Pediatrics (Under 72 years of age): 10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 7 days.

Severe Initial Clinical Episodes of Herpes Genitalis:

Adults and Adolescents (72 years of age and older): 5 mg/kg infused at a constant rate over 1 hour, every 8 hours for 5 days.

Herpes Simplex Encephalitis:

Adults and Adolescents (12 years of age and older): 10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 10 days.

Pediatrics (3 months to 12 years of age): 20 mg/kg infused at a constant rate over 1 hour, every 8 hours for 10 days.

Neonatal Herpes Simplex Virus Infections (Birth to 3 months): 10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 10 days. In neonatal herpes simplex infections, doses of 15 mg/kg or 20 mg/kg (infused at a constant rate over 1 hour every 8 hours) have been used; the safety and efficacy of these doses are not known.

Varicella Zoster Infections: Zoster in Immunocompromised Patients:

Adults and Adolescents (12 years of age and older): 10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 7 days.

Pediatrics (under 12 years of age): 20 mg/kg infused at a constant rate over 1 hour, every 8 hours for 7 days.

Obese Patients: Obese patients should be dosed at the recommended adult dose using Ideal Body Weight.

ZOVIRAX (acyclovir sodium) for Injection

Patients with Acute or Chronic Renal Impairment: Refer to DOSAGE AND ADMINISTRATION section for recommended doses, and adjust the dosing interval as indicated in Table 5.

Table 5: Dosage Adjustments for Patients with Renal Impairment

Creatinine Clearance (mL/min per 1.73 m ²)	Percent of Recommended Dose	Dosing Interval (hours)
>50	100%	8
25 - 50	100%	12
10-25	100%	24
0-10	50%	24

Hemodialysis: For patients who require dialysis, the mean plasma half-life of acyclovir during hemodialysis is approximately 5 hours. This results in a 60% decrease in plasma concentrations following a 6-hour dialysis period. Therefore, the patient's dosing schedule should be adjusted so that an additional dose is administered after each dialysis.

Peritoneal Dialysis: No supplemental dose appears to be necessary after adjustment of the dosing interval.

Method of Preparation: Each 10-mL vial contains acyclovir sodium equivalent to 500 mg of acyclovir. Each 20-mL vial contains acyclovir sodium equivalent to 1000 mg of acyclovir. The contents of the vial should be dissolved in Sterile Water for Injection as follows:

Contents of Vial	Amount of Diluent
500 mg	10 mL
1000 mg	20 mL

The resulting solution in each case contains 50 mg acyclovir per mL (pH approximately **11**). Shake the vial well to assure complete dissolution before measuring and transferring each individual dose. The reconstituted solution should be used within 12 hours. Refrigeration of reconstituted solution may result in the formation of a precipitate which will redissolve at room temperature.

DO NOT USE BACTERIOSTATIC WATER FOR INJECTION CONTAINING BENZYL ALCOHOL OR PARABENS.

Administration: The calculated dose should then be removed and added to any appropriate intravenous solution at a volume selected for administration during each 1-hour infusion. Infusion concentrations of approximately 7 mg/mL or lower are recommended. In clinical studies, the average 70-kg adult received between 60 and 150 mL of fluid per dose. Higher concentrations (e.g., 10 mg/mL) may produce phlebitis or inflammation at the injection site upon inadvertent extravasation. Standard, commercially available electrolyte and glucose solutions are suitable for intravenous administration; biologic or colloidal fluids (e.g., blood products, protein solutions, etc.) are not recommended.

Once diluted for administration, each dose should be used within 24 hours.

HOW SUPPLIED: 10-mL sterile vials, each containing acyclovir sodium equivalent to 500 mg of acyclovir, tray of 10 (NDC 0173-0995-01).

20-mL sterile vials, each containing acyclovir sodium equivalent to 1000 mg of acyclovir, tray of 10 (NDC 0173-0952-01).

Store at 15° to 25°C (59° to 77°F).

ZOVIRAX (acyclovir sodium) for Injection

GlaxoWellcome

Manufactured by
Catalytica Pharmaceuticals, Inc.
Greenville, NC 27834
for Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

June 1998

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